Protocol Title: VRC 614 (000536): A Phase 1, Dose Escalation, Open-Label Clinical Trial with Experimental Controlled Human Malaria Infections (CHMI) to Evaluate Safety and Protective Efficacy of an Anti-Malaria Human Monoclonal Antibody, VRC-MALMAB0114- 00-AB (L9LS), in Healthy, Malaria-Naive Adults

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PRINCIPAL INVESTIGATOR: Richard Wu, MD

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STUDY SITE: NIH / NIAID / VRC / Vaccine Evaluation Clinic (VEC)

Cohort: *Healthy volunteer*

Consent Version: *Version 2.0, November 3, 2021*

WHO DO YOU CONTACT ABOUT THIS STUDY?

Principal Investigator: Richard Wu, MD, [redacted]

Study Coordinator: Floreliz Mendoza, RN, [redacted]

KEY INFORMATION ABOUT THIS RESEARCH

The purpose of this consent form is to give you information to help you decide if you would like to be part of a research study at the National Institutes of Health (NIH). The decision to participate is your choice. This section provides information we believe is most helpful and important to you in making your decision. Additional information that may help you decide can be found in other sections of the document.

This is a study of an experimental drug called "L9LS". L9LS is a monoclonal antibody that targets malaria. **L9LS has not been tested in humans before this study**. We do not know if L9LS will protect you from malaria infection. There is no malaria in L9LS, so you cannot get the infection just by taking the experimental drug. You should not assume L9LS will protect you from malaria if you travel to a place where there is a risk of infection.

The main purpose of this study is to see if L9LS is safe and how your body responds to the antibody. This is the first time that L9LS will be given to people, and we do not know how your body will respond. We will follow everyone who gets L9LS for about 24 weeks.

If you have side effects from L9LS, we expect them to be like those that occur with other antibody products. These side effects include fever, chills, shaking, nausea, diarrhea, vomiting, pain, headache, dizziness, and tiredness. They usually occur within the first 24 hours after the antibody is given. Some antibody products have a risk of serious allergic reactions that can be life threatening. Although rare, other side effects that may occur are trouble breathing, itchiness, rash, hives, swelling, or chest pain, and you must reach out to the study clinicians right away if you have any of these serious side effects.

Another purpose of this study is to test if L9LS prevents you from getting malaria when you are bitten by mosquitoes that carry live malaria parasites. This is called a "malaria challenge" or a

controlled human malaria infection (CHMI). You must be available on the day of the CHMI if you are in a group taking part in the CHMI. Each person who takes part in the CHMI may get malaria infection, and we will follow everyone afterward for about 7 weeks. The CHMI will include participants who get a dose of L9LS and "control" participants who do not get L9LS.

Starting 7 days after the CHMI, you must come to the clinic every day for 11 days to be checked for malaria parasites through a blood test. Testing is done every day so that the level of malaria in your blood does not get to dangerous levels. **After the CHMI, it is important that you come to the clinic for your scheduled visits so that the level of malaria parasites in your blood does not increase to dangerous levels**.

At the first sign of malaria infection in your blood, we will treat you with a medication that will cure you. Even if the blood test is never positive, all who take part will get treated with a malaria medication at Day 21 after CHMI. We take this step to make sure that everyone is cured of malaria. The drugs that treat malaria may cause some side effects. Once you are treated, you will not be at risk for recurrence/reactivation of the infection from the CHMI. If you do not take part in the CHMI, you will not be at greater risk of getting malaria infection and will not need drugs that treat malaria.

During the study, we will collect blood samples from you. Some of your blood will be stored for future research. You will be compensated for your time and inconvenience for taking part in this study.

The study will last about 2 to 6 months, depending on your study group. During this time, you must use an effective form of birth control if able to become pregnant, must not travel to a malaria region, must not take antibiotic drugs starting 4 weeks before the beginning of the CHMI and during the CHMI (unless prescribed by a physician, in which case the study team must be notified) or donate blood for 3 years following participation in CHMI. These safety measures are further described below. All clinical study visits will take place at the NIH Clinical Center in Bethesda, Maryland. The CHMI will take place at the Walter Reed Army Institute of Research facility in Silver Spring, Maryland, and is also supported by the U.S. Department of Defense (DOD).

The remaining document will now describe the research study in more detail. This information should be considered before you make your choice. Members of the study team will talk with you about the information in this document. Some people have personal, religious, or ethical beliefs that may limit the kinds of medical or research interventions in which they would want to participate. Take the time you need to ask any questions and discuss this study with NIH staff, and with your family, friends, and personal health care providers.

IT IS YOUR CHOICE TO TAKE PART IN THE STUDY

You may choose not to take part in this study for any reason. If you join this study, you may change your mind and stop participating in the study at any time and for any reason. In either case, you will not lose any benefits to which you are otherwise entitled. However, to be seen at the NIH, you must be taking part in a study or are being considered for a study. If you do choose to leave the study, please inform your study team to ensure a safe withdrawal from the research.

WHY IS THIS STUDY BEING DONE?

Malaria is a disease that affects more than 250 million people throughout the world. The parasites that cause malaria are known as *Plasmodium*. They live in the mosquito saliva and are injected into the skin when a mosquito bites a human. This can cause malaria infection. Malaria occurs in most tropical parts of the world including Africa, Southeast Asia and South America. It is a serious threat to the local populations, to travelers and to military personnel stationed overseas. Although there are medicines to treat malaria, there is no vaccine that fully prevents infection and treatment is not easy to get in many areas of the world. If malaria is not treated right away, it can become a serious and sometimes deadly disease. If it is treated right away, it can be completely cured.

The purpose of this research study is to test a drug that could prevent malaria infection in humans called L9LS. L9LS is considered investigational, which means that it has not been approved by the U.S. Food and Drug Administration (FDA) to prevent malaria infection. It is a monoclonal antibody (mAb) that targets the parasites that cause malaria. Antibodies are naturally made by the immune system to fight infection by blocking germs (bacteria and parasites) like malaria. Monoclonal means that all the antibodies in L9LS are exactly the same.

L9LS was developed at the Vaccine Research Center (VRC) at NIH. It was made in a laboratory and looks like an antibody that your own body could make. It has shown promise for prevention of malaria in laboratory and animal studies, but it has not yet been studied in humans.

This is the first study to give L9LS to humans. We do not know if L9LS will protect you from malaria infection. You cannot get malaria from L9LS because there is no malaria in it. You should not assume L9LS will protect you from malaria.

The purpose of this research study is to see if L9LS is safe and how your body responds to it. We will give you a dose of L9LS and measure how much of it stays in your body over time. We also want to see the differences between getting L9LS as an infusion in a vein in your arm (intravenously, IV) as an injection under the skin (subcutaneously, SC) or as an injection into a muscle (intramuscularly, IM).

In this study, you will be exposed to malaria through bites from mosquitos infected with malaria parasites, if you are in Groups 1-5. This is called a "malaria challenge" or a "Controlled Human Malaria Infection" (CHMI).We do this to find out if L9LS prevents you from getting malaria after you are bitten by the infected mosquitoes in a controlled setting. We will monitor you closely and test your blood every day for many days to see if you get infected with malaria. Even if your test is negative, we will give everyone malaria treatment by 21 days after CHMI.

We are asking you to join this research study because you are a healthy adult between the ages of 18 and 50 who has never been infected with malaria. If you are in Groups 1-5, you must be willing to take part in the CHMI and comply with follow-up requirements after CHMI to be in this study. If you take part in the CHMI, you must also agree not to travel to a malaria endemic region during the whole study and not to donate blood to a blood bank for 3 years after CHMI.

WHAT WILL HAPPEN DURING THE STUDY?

This study has 6 groups as shown in the Study Schema table below. Groups 1, 2, 3, 4, and 6 will get different doses and/or routes of L9LS. Most people who get L9LS will get it by infusion into a vein (IV). Some people will get L9LS into the fat under the skin (SC) or into the muscle (IM).

A group of people called "control" participants will not get the study product but will take part in the CHMI. This group helps us make sure the mosquitos can infect people.

VRC 614 Study Schema				
Group	Subjects	L9LS Administration		CHMI
		Dose (mg/kg)	Route	
1	5	1	IV	X
2	4	5	IV	X
3	5	5	SC	X
4	4	20	IV	X
5	6[1]	Control		X
6	5	5	IM	N/A
Total	29	[1]Two (2) additional control subjects will be enrolled as CHMI back-ups		

If you decide to take part in this study, you will be asked to review and agree to this informed consent form and the procedures outlined within it. You will have completed the screening process which includes a physical exam and review of your medical history, vital signs and laboratory results. You must be healthy and qualify for enrollment before you can take part in this study.

The study will start with enrollments of people to the lowest dose of L9LS by IV and SC routes (1 mg/kg IV (Group 1) and 5 mg/kg SC (Group 3)). The next groups, 5 mg/kg IV (Group 2) and 20 mg/kg IV (Group 4), will open after the study team reviews available safety data and agrees that there are no safety concerns at the lower IV doses. Group 5 can be enrolled at any time. Group 6 will enroll after the IV and SC groups have received the study product and have undergone CHMI. Groups 1-5 will take part in the CHMI.

If you are in Group 5, you will be a control participant and will not get a dose of L9LS. After enrollment, we will check your health and draw your blood before the CHMI.

If you are female and able to become pregnant, you must use an effective method of birth control for the entire study. You will be given a pregnancy test before you get any dose of L9LS and before the CHMI. If you are pregnant, we will not give you L9LS and you cannot take part in the CHMI.

L9LS ADMINISTRATION

You will be in the clinic for about 8 hours on the day L9LS is given.

- Intravenous (IV) Dosing (Groups 1, 2, 4): We will place an IV line (thin tube) in a vein in your arm. The IV line will be attached to a bag that has L9LS mixed with a liquid called "normal saline" or salt water. It will flow into your vein for about 30 minutes. If you have side effects during the infusion, it may be slowed down or stopped as needed. At the end of your infusion, we will monitor you for any side effects. If you are the first person to get the first of a new dose level, you will be monitored for at least 2 hours. Everyone else will be monitored for at least 1 hour after getting L9LS.

  We will also place an IV line in your other arm for blood collection during the visit to avoid sticking you with a needle multiple times. We will draw your blood before and right after the infusion, and then 3 more times during the 4-6 hours after the infusion.

You will be allowed to go home about 4-6 hours after the infusion, as long as you do not have concerning side effects. If you have side effects, we will treat them. You will need to come back to the clinic 2 times during the same week for blood draws.

- Subcutaneous (SC) Dosing (Group 3): We will use a small needle to inject L9LS into the fatty tissue of your belly. We may use your arm or thigh area instead of your belly if those sites are more appropriate for your body. You will get 1 or 2 injections to get the full dose of L9LS. If you are the first person to get L9LS in this group, you will be monitored for at least 2 hours. Everyone else will be monitored for at least 1 hour after getting L9LS. If there are no safety concerns, you will be allowed to leave the clinic after the safety check. You will need to come back to the clinic3 times during the same week for blood draws.
- Intramuscular (IM) Dosing (Group 6): We will use a needle to inject L9LS into the muscle of your upper arm and/or thigh. You will get 2 to 4 injections to get the full dose of L9LS. If you are the first person to get L9LS in this group, you will be monitored for at least 2 hours. Everyone else will be monitored for at least 1 hour after getting L9LS. If there are no safety concerns, you will be allowed to leave the clinic after the safety check. You will need to come back to the clinic 3 times during the same week for blood draws.

We will give you a thermometer so that you can check your temperature every day for 7 days after you get L9LS. You will need to record your highest temperature daily and tell us about any symptoms you have. We will also give you a measuring tool so that you can measure any redness, swelling, or bruising you may have at the injection site. You will get a password to a secure website to record this information. If you do not have internet access, you may use a paper diary that we give you instead.

If you have any side effects or feel unwell after you get L9LS, you should tell a VRC nurse or doctor as soon as possible. You can reach the clinic staff by phone 24 hours a day. If you have symptoms, you may be asked to come into the clinic for an examination before your next scheduled visit. You may also stay overnight in the hospital, if needed. It is very important that you follow the instructions from the clinic staff

FOLLOW-UP AFTER L9LS ADMINISTRATION

The follow-up visits will last 30 minutes to 2 hours and allow us to check you for any health changes or problems. We will ask you how you are feeling and if you have taken any medications. We will measure your vital signs, and may perform a targeted physical exam based on how you are feeling. We will take about 1–11 tubes of blood (~ less than one half up to 6 tablespoons at each visit for safety and/or research tests. Blood draw volumes will be within NIH Clinical Center limits. We will tell you right away if any of your test results show a health problem. You might need to have extra clinic visits and laboratory tests if you have health changes that need to be checked.

Clinical studies follow a set schedule. This helps us answer the research questions. The visit schedule is a little flexible, but **it is important that you follow the schedule as closely as possible**. **You should try to not miss any visits.** You should contact the clinic staff as soon as possible if

you need to change the date or time of any study visit. When you complete this study, we may invite you to take part in another study for follow-up sample collection.

CONTROLLED HUMAN MALARIA CHALLENGE (CHMI) – GROUPS 1-5 ONLY

To learn if L9LS can prevent malaria infection, we will conduct a CHMI. The CHMI will be performed by U.S. Military scientists, physicians and other trained personnel who are experienced in conducting a CHMI under controlled conditions. It will take place at the Walter Reed Army Institute of Research (WRAIR) facility in Silver Spring, Maryland. The CHMI visit will last about 4 to 6 hours and begins very early in the morning.

During the CHMI, we will put mosquitoes carrying the malaria parasites into a cup. The cup is covered with nylon tulle netting and allows the mosquitoes to bite you under controlled conditions. They cannot escape from the cup. No more than 5 mosquitoes are put in the cup at one time. You will hold the cup against your arm for 5 minutes and then the mosquitos will be checked for blood feeding and presence of malaria parasites. If needed, more mosquitoes may be added until we are sure that a total of 5 mosquitoes have fed on your blood.

Follow up after the CHMI is very important so we can check your health. We know that it takes anywhere from 7-15 days to find malaria parasites in the blood. So, after the CHMI, we will call you by phone to check on you 2 times in the first week. Then, starting on day 7, you must come to the NIH Clinical Center every day for about 30-minute visits through day 17 so we can collect blood for diagnostic and research purposes. The visits may be longer if medical evaluation is needed. If you test positive for malaria, you will be treated right away with anti-malarial medication. We will also bring you back about 8 weeks after the CHMI to make sure you are cured. At day 21, anyone who still has a negative malaria test will be given antimalarial medication. This way we can make sure that anyone who might have malaria infection is treated, even if your tests are negative. If you are negative for malaria, we will call you by phone to check on you about 8 weeks after the CHMI

This type of CHMI has been done for over 35 years for many malaria studies. The mosquitoes that will be used are raised in a laboratory for CHMIs. They are infected with a specific strain of the malaria parasite (*Plasmodium falciparum*) that is known to be treatable with the anti-malaria medication we will give you. While the mosquitos are being grown, they feed on transfusion-quality human donor blood that has been screened following FDA requirements to make sure that the blood is not carrying any other infectious diseases. This type of malaria does not cause recurrent infections after you are treated.

HOW LONG WILL THE STUDY TAKE?

The study will last for about 24 weeks if you are in Groups 1, 2, 3, 4, and 6 that get L9LS. You will visit the NIH Clinical Center for about 11 or 12 study visits based on if you get L9LS by IV or SC/IM, respectively, and up to 15 visits for the CHMI follow-up if you are taking part in the CHMI. If you are in Group 5, which does not receive L9LS, the study will last for about 7 weeks after the CHMI. We will discuss the exact schedule and location of these visits with you.

HOW MANY PEOPLE WILL PARTICIPATE IN THIS STUDY?

We plan to enroll about 29 people. This includes about 23 people who will get L9LS and about 6 control participants. We may enroll up to 40 people if needed to complete the study and this includes 2 back-up control participants for the CHMI.

WHAT ARE THE RISKS AND DISCOMFORTS OF BEING IN THE STUDY?

POSSIBLE RISKS OF L9LS

This study is the first time that L9LS will be given to people. The information described below is taken from studies with other antibodies that are like L9LS and may work the same. Some of those antibodies are approved for use in people. Like other drugs, monoclonal antibodies can cause side effects, some of which can be serious. Most side effects occur within the first 24 hours after an antibody is given.

- Side effects to antibodies given by IV may include: fever, chills, shaking, nausea, vomiting, pain, headache, dizziness. More serious but rare side effects may occur, including trouble breathing, high or low blood pressure, itchiness, rash, hives, lip or face swelling, diarrhea, racing heart, or chest pain. These symptoms usually go away within a few minutes to hours after the product is given. We are giving L9LS at a controlled rate. If you develop symptoms while getting L9LS, tell the nurse right away. Slowing or stopping the flow rate may help improve the symptoms.
- Side effects to antibodies given by SC may include: mild itchiness, redness and/or swelling at the site of injection. Tiredness, muscle pain, and headache have also been reported. These symptoms usually go away within 1 to 2 days.
- Side effects to antibodies given IM include: mild itchiness, redness and/or swelling at the site of injection. Tiredness, muscle pain, and headache have also been reported. These symptoms usually go away within 1 to 2 days.

Some antibodies have a risk of serious allergic reactions that can be life threatening including:

- Anaphylaxis is one type of allergic reaction that may happen soon after an antibody is given. This reaction can include difficulty breathing, low blood pressure, hives, rash, or swelling in the mouth and face. This reaction is rare but can be life threatening. Participants will remain under observation in the time frame that this usually occurs.
- Serum sickness is a type of allergic reaction that may happen several days to weeks after an antibody is given. This reaction may include hives, rash, fever, enlarged lymph nodes,muscle pains, joint pains, chest discomfort or shortness of breath.

Some antibody products can increase the risk of serious infections. L9LS is not expected to increase the risk of serious infections because it attacks a parasite and does not target the human immune system.

In a lab study, L9LS attached to the salivary glands that produce saliva. This was a rare finding. We do not know if L9LS affects your salivary glands. We will be checking for any possible problems with your salivary glands during the study. If there is a concern for salivary gland

problems, we may ask an oral specialist to examine you and provide a recommendation for your care.

UNKNOWN RISKS

L9LS may have other side effects that are not yet known. Taking part in this study may affect your eligibility for future monoclonal antibody or malaria studies. We will give you any new information about risks or other information that may affect your decision to continue in the study as it becomes available. You may not donate blood while taking part in this study and you may not donate blood for one year after the date of your last dose of L9LS or three years after your last CHMI.

POSSIBLE RISKS OF IV, IM, OR SC DOSING

General risks of methods that use a needle include stinging, discomfort, pain, soreness, redness, bruising, swelling or a tiny cut at the needle insertion site.

POSSIBLE RISKS OF BLOOD DRAWING

Blood drawing may cause pain, bruising, and may cause a feeling of lightheadedness or fainting. Rarely, it may cause infection at the site where the blood is taken. An IV line will be placed in your vein for a few hours on a day L9LS is given by IV. Problems at the IV site are usually mild and may include pain, bruising, minor swelling, or bleeding. Rarely, there may be an infection, vein irritation, nerve problem, or blood clot.

POSSIBLE RISKS OF CHMI – GROUPS 1-5 ONLY

During the CHMI, you will be bitten by mosquitoes that carry live malaria parasites which cause malaria infection. We do not know if L9LS will protect people from malaria. If you did not receive any L9LS and are in the control group, you are expected to get malaria. If you get malaria, you may experience the following symptoms:

- Fever, chills, headache, dizziness, muscle aches, sweats, fatigue, insomnia
- Nausea, vomiting, stomach cramps, diarrhea
- Decrease in numbers of red blood cells, white blood cells, and platelets
- Enlarged liver or spleen

Symptoms are usually mild to moderate, but you may have some severe symptoms. You may have fevers for 1 to 3 days. You may miss time from work or school due to your illness. You will not be compensated for any loss of income for missing work. If malaria is not treated right away, it can lead to kidney, liver, heart or brain damage and death. The CHMI is considered to be safe because people are closely monitored and treated as soon as they are found to have malaria infection, but they must remain in close contact with the study team.

After the CHMI, it is important that you come to the clinic for your scheduled visits so that the level of malaria parasites in your blood does not increase to dangerous levels. From past studies we know that malaria parasites can be found in the blood anywhere from about 7 to 15 days after mosquito exposure. About half of the people infected with malaria parasites develop

fever that usually lasts less than 12 hours. Once treatment for malaria is started, the fever does not last longer than 48 hours.

Other symptoms of headache, nausea, vomiting, and loss of appetite may occur. These symptoms may last an average of 3 days, with a range of 1 to 6 days when treatment is started soon after malaria parasites are identified by blood tests. **Failure to return for testing or treatment after a CHMI can result in a serious case of malaria that is life-threatening.** For this reason, you must give the names and phone numbers of at least two emergency contacts to the study staff. We will contact them before the CHMI to confirm communication with them in case we are not able to reach you by phone, text, or email after CHMI.

Among the 2,700+ participants who have participated in a CHMI since 1971, two serious events have been reported. Both were cardiac events (chest pain) and occurred in people who got an investigational malaria vaccine. The pain was thought to be due to myocarditis (inflammation of the heart muscle). Myocarditis is a reported complication from vaccinations. Rarely, myocarditis has also been reported in association with naturally-acquired malaria infection.

These are the only two cases we know about in which a cardiac event occurred after CHMI. In the unlikely event that you develop myocarditis, you will be evaluated and followed by a cardiologist until resolution.

If you feel unwell at any time after the CHMI, you may be asked to remain in the clinic until you are checked by a study doctor. You might stay in the hospital overnight if needed.

POSSIBLE RISKS FROM TREATMENT FOR MALARIA – GROUPS 1-5 ONLY

Everyone who takes part in the CHMI will get antimalarial treatment by Day 21 after CHMI. Standard treatment for malaria takes 72 hours to complete. We will give you the medication at the first sign of infection in your blood. You should expect to have malaria symptoms for about 3 days. Only drugs approved by the U.S. FDA will be used for treatment of malaria. We will treat you with Malarone unless you have a known allergy. In that case, we would treat you with chloroquine or another suitable alternative. Any drugs given are effective in treating the type of malaria parasite used for the CHMI.

The drugs that treat malaria may also cause some side effects. Treatments and their side effects are described below:

1. The first line of treatment will be Malarone. If you get Malarone, you may have the following side effects:
    - Nausea, vomiting, abdominal pain, loss of appetite, diarrhea
    - Temporary elevation of liver function tests
    - Headache and coughing
    - Rarely, low blood count, oral irritation or ulcers, insomnia, fever, swelling, rash and hair loss
2. Another backup treatment option will be chloroquine. If you get chloroquine, you may have the following side effects:
    - Nausea, vomiting, abdominal pain, diarrhea, dizziness, sleep

disturbances and photosensitivity
- Headache, blurred vision, ringing in ears
- Itching, skin rash, and make conditions of psoriasis (itchy skin rash) and porphyria (rare disturbance of metabolism that can be seen as disorders of the skin or other organs) worse
- Long term use can cause permanent eye damage or deafness, but you will only be receiving a short course of treatment
- Rarely, there may be changes in electrocardiograms (test of heart's electrical activity) and low blood pressure

If you need treatment with any other antimalarial drug, we will give you information about the side effects of that drug. You can also take over-the-counter medicine, like acetaminophen (Tylenol) and/or ibuprofen for fever, headache or other symptoms of malaria.

MOSQUITO BITE SITE REACTIONS – GROUPS 1-5 ONLY

Local, allergic reactions are common after mosquito bites. You may have itching and raised, red swelling at the sites of the bites. These reactions usually develop quickly, go away 1 to 4 days after a mosquito bite, and do not need treatment. So far, no severe allergic reactions to mosquito bites have been reported in prior CHMI studies. You will be observed for 30 minutes after the last mosquito bite. We will check the bite area and watch for any severe allergic signs. We may give you a steroid cream to use on the skin reactions.

POSSIBLE RISKS FROM STORED SAMPLES

There is a small chance that information from your medical records could be given to someone who should not get it without your permission. It is possible for someone to use that information to discriminate against you when you apply for insurance or employment. Similar problems may occur if you give information about yourself or agree to have your medical records released.

POSSIBLE RISKS OF DATA SHARING

Information in the shared databases could be linked back to you and used to discriminate against you or your family. State and federal laws provide some protections against genetic and preexisting conditions discrimination.

POSSIBLE RISKS RELATED TO PREGNANCY

If you are able to become pregnant, we will do a pregnancy test before beginning this study. We will also give you a pregnancy test before you get L9LS and before CHMI. You must use effective birth control methods and try not to become pregnant while taking part in this study. If you become pregnant, there may be unknown risks to the fetus or unborn child, or risks that we did not anticipate. There may be long-term effects of the treatment being studied that could increase the risk of harm to a fetus. You must tell the study doctor if your birth control method fails while you are in the study. If you think or know you have become pregnant while taking part in this research study, please contact the research team member identified at the top of this document as soon as possible. You should not plan to become pregnant until you have completed participation in this study.

SAFETY MEASURES YOU SHOULD USE AS A PARTICIPANT IN THE STUDY

You should not expect L9LS to protect you from malaria in the future. You should assume that you are not protected from malaria. After leaving the study, you should follow your physician's instructions to prevent malaria infection. We also ask that you follow our instructions below:

- Travel: Do not travel outside the local area from the CHMI through 28 days after. Before or after this point, please let the study staff know about planned travels so we can schedule your visits and have contact information before you travel. We ask that you not travel to any areas with malaria during the entire period of the study. Country-specific informationcan be provided. This does not apply to Group 6.
- Use of Antibiotics: Avoid taking antibiotics starting 4 weeks before the CHMI and during the CHMI unless prescribed by a physician. Please notify the study team immediately if an antibiotic is prescribed for you or if you consider taking an antibiotic during the course of the study. This does not apply to Group 6.
- Blood Donation: You will not be permitted to donate blood for transfusion purposes while in the study, for 1 year after your L9LS administration and for 3 years after the CHMI. To make sure that blood is safe for donation, blood banks will not accept blood donations for 1 year after exposure to an investigational product (L9LS) and for 3 years from anyone who is infected with or treated for malaria.
- Mosquito Avoidance: For two weeks after the CHMI you should practice mosquito avoidant behaviors. This includes covering your skin when outside, avoiding outdoors at times mosquitoes are active (dusk, evening, dawn), using insect repellants appropriately on yourself and your clothes, and maintaining effective mosquito barriers in your home such as screen doors and windows. Clinical staff will cover these with you again in detail during the CHMI process. This does not apply to Group 6.

WHAT ARE THE BENEFITS OF BEING IN THE STUDY?

You will not benefit from being in this study.

Are there any potential benefits to others that might result from the study?

In the future, other people might benefit from this study because the information may help us learn more about preventing and treating malaria infection. Results from this study may also be used to help develop new products that target malaria or other infectious diseases in the future.

WHAT OTHER OPTIONS ARE THERE FOR YOU?

Before you decide whether or not to be in this study, we will discuss other options that are available to you. Instead of being in this study, you could choose not to take part. You may be eligible for other VRC studies.

DISCUSSION OF FINDINGS

New information about the study

If we find out any new information that may affect your choice to participate in this study, we will get in touch with you to explain what we have learned. This may be information we have learned while doing this study here at the NIH or information we have learned from other scientists doing similar research in other places.

Return of research results

At each visit you will be checked for any health changes or problems. Blood will be drawn at almost every study visit to either check on your health or collect samples for research. You will be told right away by phone call, text, or in person in the clinic if any of your test results show a health problem.

After the CHMI, we will draw your blood to test for malaria parasites. You will be told right away by phone, or in person in the clinic if we find that you have malaria infection.

We will use some of the blood samples to study how long L9LS remains in your body and if your body develops an immune response to L9LS and to the CHMI. We will also study the malaria parasites that we may find in your bloodstream after the CHMI if you get malaria infection. These tests are for research purposes only and are not for checking on your health. We will not give you these results.

The results of this study may be reported in medical journals, on the internet or at scientific meetings. We will give you information about how to find the study results once they are available.

EARLY WITHDRAWAL FROM THE STUDY

You may be removed from the research study by the researcher for any of the following reasons:

- Not keeping appointments or following study procedures;
- Getting a serious illness that needs ongoing medical care;
- Enrolling in another research study at the same time you are in this study;
- Becoming pregnant;
- The study is stopped or cancelled;
- The researcher believes that it is in your best interest to remove you from the study.
- The study is stopped by regulatory agencies, the study sponsor or study investigators. If this happens, we will tell you why.

You can stop taking part in the study at any time. However, if you decide to stop taking part in this study, you will be asked to keep follow up visits so we can check your health, especially if you got a dose of L9LS or take part in the CHMI. We may stop collecting samples that are for research purposes only.

We don't know if you will get malaria after the CHMI. If you choose to stop the study after the CHMI and before completion of monitoring for malaria infection, you will need to be treated for malaria by the study doctor regardless of whether you develop symptoms of malaria or parasites in your blood.

STORAGE, SHARING AND FUTURE RESEARCH USING YOUR SPECIMENS AND DATA

Will your specimens or data be saved for use in other research studies?

As part of this study, we are obtaining specimens and data from you. We will remove all the identifiers, such as your name, date of birth, address, or medical record number and label your specimens and data with a code so that you cannot easily be identified. However, the code will be linked through a key to information that can identify you. We plan to store and use these specimens and data for studies other than the ones described in this consent form that are going on right now, as well as studies that may be conducted in the future. These studies may provide additional information that will be helpful in understanding malaria, or other diseases or conditions. This could include studies to develop other research tests, treatments, drugs, or devices, that may lead to the development of a commercial product by the NIH and/or its research or commercial partners. There are no plans to provide financial compensation to you if this happens. Also, it is unlikely that we will learn anything from these studies that may directly benefit you.

By agreeing to take part in this study, you give permission for your coded specimens and data to be stored and used for future research as described above.

Will your specimens or data be shared for use in other research studies?

We may share your coded specimens and data with other researchers. If we do, while we will maintain the code key, we will not share it, so the other researchers will not be able to identify you. They may be doing research in areas that are similar to this study or in other unrelated areas. These researchers may be at NIH, other research centers and institutions, or commercial entities.

By agreeing to take part in this study, you give permission for your coded specimens and data to be shared with other researchers and used by these researchers for future research as described above.

If you change your mind and do not want us to store and use your specimens and data for future research, you should contact the research team member identified at the top of this document. We will do our best to comply with your request but cannot guarantee that we will always be able to destroy your specimens and data. For example, if some research with your specimens and data has already been completed, the information from that research may still be used. Also, for example, if the specimens and data have been shared already with other researchers, it might not be possible to withdraw them.

In addition to the planned use and sharing described above, we might remove all identifiers and codes from your specimens and data and use or share them with other researchers for future research at the NIH or other places. When we or the other researchers access your anonymized data, there will be no way to link the specimens or data back to you. We will not contact you to ask your permission or otherwise inform you before we do this. We might do this even if you answered "no" to the above questions. If we do this, we would not be able to remove your specimens or data to prevent their use in future research studies, even if you asked, because we will not be able to tell which are your specimens or data.

NIH policies require that your clinical and other study data be placed in an internal NIH database that is accessible to other NIH researchers for future research. Usually, these researchers will not have access to any of your identifiers, such as your name, date of birth, address, or medical record number; and your data will be labeled with only a code. We cannot offer you a choice of whether your data to be placed in this database or not. If you do not wish to have your data placed in this database, you should not enroll in this study.

GENETIC TESTING

Some of the blood drawn from you during this study will be used for genetic tests. Some genetic tests are done in research studies to see if there are genetic difference in immune responses. Your blood sample used in these genetic tests will not have your name on it, and the results will not be in your medical record.

How long will your specimens and data be stored by the NIH?

Your specimens and data may be stored by the NIH indefinitely.

Risks of storage and sharing of specimens and data

When we store your specimens and data, we take precautions to protect your information from others that should not have access to it. When we share your specimens and data, we will do everything we can to protect your identity, for example, when appropriate, we remove information that can identify you. Even with the safeguards we put in place, we cannot guarantee that your identity will never become known, or someone may gain unauthorized access to your information. New methods may be created in the future that could make it possible to re-identify your specimens and data.

PAYMENT

Will you receive any type of payment for taking part in this study?

You will be compensated for your time and inconvenience by the NIH Clinical Research Volunteer Program per NIH policies and guidelines. It is possible that you may have some expenses that are not covered by the compensation provided.

The compensation for specific study visits is as follows:

- $430 for the study visit that includes IV administration of L9LS
- $375 for the study visit that includes SC or IM administration of L9LS $455 for the malaria challenge (CHMI) with pre-CHMI clinic visit and activities
- $25 total for the timely completion of all 7 days of an electronic diary
- $200 for a scheduled follow-up visit that includes blood draw
- $85 for all other clinic visits that do not include blood draws

Total compensation for completion of all study visits including CHMI is between $4195 and $5950 if you get L9LS by IV and between $4340 and $6140 if you get L9LS by SC. Compensation for the IM group is around $2800. Compensation for CHMI visits for the control group is between about $1625 and $3425. The total compensation you get is based on the number and type of study

visits you complete. If you are unable to finish the study, you will get compensation only for the study visits you completed.

You will get the compensation about 2 weeks after each completed visit by direct deposit into a bank account that you specify to the Volunteer Payment Office.

The study team will collect social security numbers from research participants for purposes of compensation. Participants can withhold their social security numbers and still participate in the research study; however you may not be able to receive compensation if you do so.

With few exceptions, study compensation is considered taxable income that is reportable to the Internal Revenue Service (IRS). A "Form 1099-Other Income" will be sent to you if your total payments for research participation are $600 or more in a calendar year. If you have unpaid debt to the federal government, please be aware that some or all of your compensation may be automatically reduced to repay that debt on your behalf.

REIMBURSEMENT

Will you receive reimbursement or direct payment by NIH as part of your participation?

This study does not offer reimbursement for participants, or payment of, hotel, travel, or meals.

COSTS

Will taking part in this research study cost you anything?

NIH does not bill health insurance companies or participants for any research or related clinical care that you receive at the NIH Clinical Center.

CONFLICT OF INTEREST (COI)

The NIH reviews NIH staff researchers at least yearly for conflicts of interest. This process is detailed in a COI Guide. You may ask your research team for a copy of the COI Guide or for more information. Members of the research team who do not work for NIH are expected to follow these guidelines or the guidelines of their home institution, but they do not need to report their personal finances to the NIH.

The NIH and the research team for this study have developed the investigational product, L9LS, being used in this study. This means it is possible that the results of this study could lead to payments to NIH. By law, the government is required to share such payments with the employee inventors. You will not receive any money from the development of L9LS.

CLINICAL TRIAL REGISTRATION AND RESULTS REPORTING

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results, once they are available. You can search this website at any time.

CONFIDENTIALITY PROTECTIONS PROVIDED IN THIS STUDY

Will your medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The NIH and other government agencies, like the Food and Drug Administration (FDA), which are involved in keeping research safe for people.
- NIH Intramural Institutional Review Board
- The study Sponsor (VRC) or their agent(s)
- United States Army Medical Research and Development Command (USAMRDC) representatives

The researchers conducting this study and the NIH follow applicable laws and policies to keep your identifying information private to the extent possible. However, there is always a chance that, despite our best efforts, your identity and/or information about your participation in this research may be inadvertently released or improperly accessed by unauthorized persons.

In most cases, the NIH will not release any identifiable information collected about you without your written permission. However, your information may be shared as described in the section of this document on sharing of specimens and data, and as further outlined in the following sections.

Further, the information collected for this study is protected by NIH under a Certificate of Confidentiality and the Privacy Act.

Certificate of Confidentiality

To help us protect your privacy, the NIH Intramural Program has received a Certificate of Confidentiality (Certificate). With this certificate, researchers may not release or use data or information about you except in certain circumstances.

NIH researchers must not share information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if requested by a court.

The Certificate does not protect your information when it:

1. is disclosed to people connected with the research, for example, information may be used for auditing or program evaluation internally by the NIH; or
2. is required to be disclosed by Federal, State, or local laws, for example, when information must be disclosed to meet the legal requirements of the federal Food and Drug Administration (FDA);
3. is for other research;
4. is disclosed with your consent.

The Certificate does not prevent you from voluntarily releasing information about yourself or your involvement in this research.

The Certificate will not be used to prevent disclosure to state or local authorities of harm to self or others including, for example, child abuse and neglect, and by signing below you consent to those disclosures. Other permissions for release may be made by signing NIH forms, such as the Notice and Acknowledgement of Information Practices consent.

Privacy Act

The Federal Privacy Act generally protects the confidentiality of your NIH medical information that we collect under the authority of the Public Health Service Act. In some cases, the Privacy Act protections differ from the Certificate of Confidentiality. For example, sometimes the Privacy Act allows release of information from your record without your permission, for example, if it is requested by Congress. Information may also be released for certain research purposes with due consideration and protection, to those engaged by the agency for research purposes, to certain federal and state agencies, for HIV partner notification, for infectious disease or abuse or neglect reporting, to tumor registries, for quality assessment and medical audits, or when the NIH is involved in a lawsuit. However, NIH will only release information from your medical record if it is permitted by both the Certificate of Confidentiality and the Privacy Act.

POLICY REGARDING RESEARCH-RELATED INJURIES

The NIH Clinical Center will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the NIH, the NIH Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

FOR INJURIES RELATED TO CHMI

If you are injured because of your participation in this research during the CHMI and you are a DOD healthcare beneficiary (e.g., active duty in the military, military spouse or dependent, retiree), you are entitled to medical care for your injury within the DOD healthcare system, as long as you remain a DOD healthcare beneficiary.

If you are injured because of your participation in this research during the CHMI and you are not a DOD healthcare beneficiary, you are entitled to medical care for your injury at a DOD hospital or clinic, but such care for your injury at DOD hospitals or clinics may be time-limited, and your insurance may be billed. It cannot be determined in advance which DOD hospital or clinic will provide care. If you obtain care for research-related injuries outside of a DOD hospital or clinic, you or your insurance will be responsible for medical expenses.

For DOD healthcare beneficiaries and non-DOD healthcare beneficiaries: Transportation to and from hospitals or clinics will not be provided. No reimbursement is available if you incur medical expenses to treat research-related injuries. No compensation is available for research-related injuries. You are not waiving any legal rights. If you believe you have sustained a research-related injury, please contact the Principal Investigator (PI). If you have any questions, please contact the PI.

PROBLEMS OR QUESTIONS

If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, Richard Wu, MD at [redacted] Other researchers you may call are: Floreliz Mendoza, RN or Lasonji Holman, FNP at [redacted] You may also call the NIH Clinical Center Patient Representative at [redacted] or the NIH Office of IRB Operations at [redacted] if you have a research-related complaint or concern.

CONSENT DOCUMENT

Please keep a copy of this document in case you want to read it again.

Adult Research Participant: I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I consent to participate in this study.

Signature of Research Participant	Print Name of Research Participant	Date

Investigator:

Signature of Investigator	Print Name of Investigator	Date

Witness should sign below if either:

1. **A short form consent process has been used to enroll a non-English speaking subject or**
2. **An oral presentation of the full consent has been used to enroll a blind or illiterate subject**

Signature of Witness	Print Name of Witness	Date

NIH ADMINISTRATIVE SECTION TO BE COMPLETED REGARDING THE USE OF AN INTERPRETER:

____ An interpreter, or other individual, who speaks English and the participant's preferred language facilitated the administration of informed consent and served as a witness. The investigator obtaining consent may not also serve as the witness.

____ An interpreter, or other individual, who speaks English and the participant's preferred language facilitated the administration of informed consent but did not serve as a witness. The name or ID code of the person providing interpretive support is: _____.